REMARKS

Entry of the foregoing amendment, and further favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested. It is noted that the foregoing amendment does not affect the substance of the claims, but is merely formal in nature, and places the application in better form for an appeal should an appeal become necessary. In particular, claim 1 has been amended for better grammatical form. No new matter has been introduced by way of the instant amendment.

As correctly indicated in the Office Action Summary, claims 1-9 are pending in the application and are under consideration; claims 1-9 stand rejected.

Rejections under 35 U.S.C. § 103

Claim 1 stands rejected under 35 U.S.C. § 103 as allegedly unpatentable over Kim et al., WO 0195927 ("Kim") in view of Gallucci et al., FASEB J, 14:2525-31, 2000 ("Gallucci") for the reasons set forth in the Office Action mailed September 27, 2005. This rejection is respectfully traversed.

Applicant has pointed out that to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MANUAL OF PATENT EXAMINATION PROCEDURE ("M.P.E.P. § 2143").

Applicant submits that the prior art fails to provide either the requisite motivation or reasonable expectation of success to modify and combine the references as proposed by the Office.

Applicant reminded the Office that with regard to whether the prior art provides the requisite motivation and reasonable expectation of success to combine and/or modify references, reliance on hindsight is impermissible. The Office replied that any judgment on obviousness is necessarily a reconstruction based on hindsight reasoning, and that such hindsight is acceptable so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made.

The prohibition on hindsight to which Applicant refers relates particularly to selective consideration of isolated conjectures that may appear in cited references. A determination under 35 U.S.C. § 103 should rest on all the evidence and should not be influenced by any earlier conclusion. *See, e.g., In re Piasecki*, 745 F.2d 1468, 1472-73, 223 USPQ 785, 788 (Fed. Cir. 1984); *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990); M.P.E.P. § 2144.08. That is, every teaching or suggestion of the prior art must be considered in light of the whole context of the state of the art at the time the invention was made.

Applicants respectfully submit that the error that the Office has made in this case is to selectively consider only those parts of the prior art that tend to support the Office's preconceived conclusion. The Office is reminded that it is impermissible to view the prior art in such a manner as to select from the art only those facts which may be modified and then utilized to reconstruct applicant's invention from such prior art. *Interconnect Planning Corp. v. Feil*, 150 U.S.P.Q. 54, 57 (C.C.P.A 1966); *In re Shuman*, 774 F.2d 1132, 1142-3, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985).

Upon consideration of the documents as a whole, Kim and Galluci fail to provide either the requisite motivation or reasonable expectation of success to modify and combine the references as proposed by the Office.

The teaching of Kim would in fact have lead one of ordinary skill away from the present invention. For example, the Office appears to have ignored that Kim teaches that EMAP II is expected to have a therapeutic potential as an anti-angiogenic factor. *See* Kim at 1. Although Kim does not disclose the anti-angiogenic effect of p43, p43 would be expected to have the anti-angiogenic effect, because, as noted by the Office, EMAP II is a C-terminal domain of p43. Experimental results supporting that p43 has the anti-angiogenic effect can be found in Example 4 of Korean Patent Application No. 10-2001-33399 that was based on and claimed priority of Kim. (English language translation attached as Exhibit A). In the Korean Patent Application, it is disclosed that p43 has more effective anti-angiogenic activity than EMAP II.

The teaching in Kim suggesting that p43 has anti-angiogenic activity would have indicated that it could inhibit wound healing to one of ordinary skill in the art, contrary to the presently claimed methods. In general, wound healing is a reaction of tissue against damage inflicted upon the tissue, and it is known as a complex biological process comprising chemotaxis, cell differentiation and replication, synthesis of matrix protein, angiogenesis and reconstitution of wound, as a series of tissue repair processes. *See* SPECIFICATION at 1. The formation of new blood vessels is necessary to sustain the newly formed granulation tissue in wound healing process. Therefore, the disclosure of Kim would tend to teach against the presently claimed methods.

Furthermore, Kim discloses additional properties of p43 that would tend to suggest that p43 would inhibit wound healing. For example, Kim discloses that p43 and EMAP II

induce release of TNF-α having cytokine activity. TNF-α is a cytokine known to inhibit wound healing. *See, e.g.,* Rapala et al. (*Eur Surg Res.* 23(5-6):261-8, 1991) at Abstract; and Rapala K (*Ann Chir Gynaecol* Suppl. 211:1-53, 1996) at Abstract (Abstracts attached as Exhibit B).

Considering the teachings of Kim as a whole in the context of the state of the art, and not selectively picking out of context only those facts that might be combined with Gallucci, it is clear that there would have been no motivation to modify Kim to arrive at the presently claimed method.

Furthermore, the reliance by the Office on the limited teaching of Gallucci, illustrates the extent to which the Office has selectively considered only those random facts of the prior art that might be used to reconstruct the presently claimed invention. The results reported by Gallucci suggest only that IL-6 is a cytokine associated with wound healing to the extent that its absence causes a deficiency in healing. Gallucci does not teach or suggest that additional IL-6 would stimulate wound healing in an IL-6 normal background. Any such suggestion has must have been derived by the Office using hindsight, since the data presented in Gallucci does not prove the conjecture upon which the Office relies to arrive at its conclusion.

The present rejection must be the product of impermissible hindsight. To support the rejection of the presently claimed invention, the Office has selectively picked one idea out of Kim, despite the fact that the teachings of Kim taken as a whole tend to teach against the present invention, and combined this idea with a suggestion derived from Gallucci, based on a conjecture not proven by Gallucci, to arrive at the erroneous conclusion that the invention would have been obvious. This is the very sort of hindsight that the Federal Circuit and its predecessor have deemed impermissible. *See, e.g., Interconnect Planning Corp. v. Feil*, 150

U.S.P.Q. 54, 57 (C.C.P.A 1966); *In re Shuman*, 774 F.2d 1132, 1142-3, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985).

For at least the foregoing reasons, the Office has failed to set forth a prima facie case of obviousness. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 2-9 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Kim in view of Gallucci and further in view of Bennett et al., *Am J. Surg.*, 165:728-37, 1993 ("Bennett") for the reasons set forth in the Office Action mailed September 27, 2005. This rejection is respectfully traversed.

Bennett does not cure the deficiencies of Kim and Gallucci. For the reasons previously stated, when the whole teaching of Kim and Gallucci are considered, there would not have been any motivation or reasonable expectation of success in using the polypeptide of SEQ ID NO:1 in a composition for wound healing. In the absence of any motivation or reasonable expectation of success in using the polypeptide of SEQ ID NO:1 in a composition for wound healing, which could only be arrived at through an impermissible application of hindsight selectivity, a person of ordinary skill would have no reason to think that the polypeptide of SEQ ID NO:1 should be combined with any of the compounds taught by Bennett.

Therefore, the proposed combination of Bennett with Kim and Gallucci does not constitute a prima facie case of obviousness. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1, 4 and 7 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over Kim in view of Gallucci and further in view of Goddard et al., U.S. Patent No. 6,916,648 ("Goddard") for the reasons set forth in the Office Action mailed September 27, 2005. This rejection is respectfully traversed.

However, Goddard does not cure the deficiencies of Kim and Gallucci. For the reasons previously stated, when the whole teaching of Kim and Gallucci are considered, there would not have been any motivation or reasonable expectation of success in using the polypeptide of SEQ ID NO:1 in a composition for wound healing. Goddard provides no further teaching that would tend to provide a suggestion to combine Kim with Gallucci or a reasonable expectation of success that the proposed combination would be successful. In the absence of any such teaching or reasonable expectation of success, a person of ordinary skill would have no reason to think that the polypeptide of SEQ ID NO:1 should be combined with any treatment with VEGF taught by Goddard.

For at least the foregoing reasons, the proposed combination of Goddard with Kim and Gallucci does not constitute a prima facie case of obviousness. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 9, 2006

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1: Eur Surg Res. 1991;23(5-6):261-8. Links

Tumor necrosis factor alpha inhibits wound healing in the rat.

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This work was undertaken to study the effects of tumor necrosis factor-alpha (TNF-alpha/cachectin) on developing granulation tissue in rats. Cylindrical hollow sponge implants were used as an inductive matrix for the growth of granulation tissue. In the two test groups the implants were injected daily for 4 days with a solution containing either 50 or 200 ng of TNF-alpha, while the implants of the control group were treated correspondingly with phosphate-buffered saline solution only. Analyses of granulation tissue and would fluid in the sponge implants were carried out 7, 14 and 21 days after implantation. In histological specimens the ingrowth rate of granulation tissue into the sponge was significantly lower after 7 days in the group treated with 200 ng of TNF-alpha. No such an effect was observed after 14 or 21 days. After 7 days, the mean amounts of nucleic acids reflecting cellularity in the granulation tissue decreased dose-dependently, but nonsignificantly, in the groups treated with TNF-alpha. Simultaneously, the accumulation of collagen hydroxyproline of the sponge was significantly lower in the group treated with 200 ng of TNF-alpha than in the controls (-30%, one-way analysis of variance). This effect was not observed after 14 or 21 days. No significant differences were detected in the amounts of nitrogen, hexosamines and uronic acids between the groups, reflecting unchanged accumulation of glycosaminoglycans in the developing granulation tissue.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 1802728 [PubMed - Indexed for MEDLINE]

1: Ann Chir Gynaecol Suppl. 1996;211:1-53.

Links

The effect of tumor necrosis factor-alpha on wound healing. An experimental study.

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The inflammatory phase in wound healing is considered to be a preparatory process for the formation of new tissue. A monocyte-derived cytokine, tumor necrosis factor-alpha (TNF-alpha), is a highly conserved molecule known to play a major role in the pathogenesis of gram-negative shock. Besides this, previous experimental studies show that TNF-alpha may have either a beneficial or detrimental role in wound healing. The purpose of the present study was to examine the effects of TNF-alpha on developing granulation tissue in rats as well as on rat and human granulation tissue cells in culture. Subcutaneously implanted cylindrical hollow sponges were used for studying the effects of locally applied TNF-alpha on granulation tissue in rats. These implants were treated either on the day of implantation or for the first 4 or 7 days after implantation with a solution containing various amounts of TNF-alpha while the control implants were treated correspondingly with the carrier solution only. The analyses of the granulation tissue were carried out 4, 7, 14 and 21 days after implantation. In the histological specimen these sponges were cut into small pieces and stained with Weigert van Gieson to visualize collagen. The amount of granulation tissue grown into the sponge was calculated from the cross section of every sponge. For the cell culture studies fibroblasts were released from human and rat granulation tissue which was cut into small pieces and digested by collagenase and DNase in Hank's balanced salt solution. The cells were exposed to 1, 10, or 100 ng/ml of TNF-alpha and the rate of collagen synthesis was measured as synthesis of protein-bound 3H-hydroxyproline. The number of cells in the culture dishes was counted with Burger's hemocytometer after detaching the cells with trypsin treatment. As interleukin-1 (IL-1) and TNF-alpha overlap in many of their functions, the effects of lipopolysaccharide (LPS), human interleukin 1 beta (IL-1) and prostaglandin E2 (PGE2) on experimental granulation tissue in rats as well as on rat granulation tissue cells in culture were studied with the same method. After a single application of TNF-alpha into the sponge, no essential differences between the groups were detected. However, after daily applications of TNF-alpha for 4 days, an inhibitory effect on tissue repair was

observed after 4 and 7 days. Collagen formation, indicated by the hydroxyproline content of the sponge, was significantly lower in the group treated with TNF-alpha than in the controls. This effect was not observed after 14 or 21 days. These findings were confirmed in the histological samples. In the cultures of rat granulation tissue fibroblasts TNF-alpha decreased 3H-hydroxyproline production to about 75% of that in the controls and it had also a decreasing effect on pro alpha 1(I) and pro alpha 1(III) collagen mRNA levels maximally by 67% and 77% of the control level, respectively. In the cultures of human granulation tissue fibroblasts a similar inhibiting effect on the production of collagen was seen. TNF-alpha decreased the production of 3H-hydroxyproline to 56% of the control value with a dose of 100 ng/ml. Similarly, IL-1 beta decreased hydroxyproline content of granulation tissue seven days postoperatively and PGE2 decreased nonsignificantly the amounts of hydroxyproline but the steady-state levels of pro alpha 1(I) and pro alpha 1(III) collagen chain mRNAs were slightly elevated. In the IL-1 beta-treated fibroblast cultures collagen production decreased by 15% compared with that of the controls. PGE2 decreased collagen production by 34% of that in the controls. This effect could be abolished with indomethacin. Indomethacin alone stimulated collagen production by 40%. In vivo IL-1 decreases the formation of normal granulation tissue. This effect may be partly due to IL-1 stimulated secretion of PGE2.

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